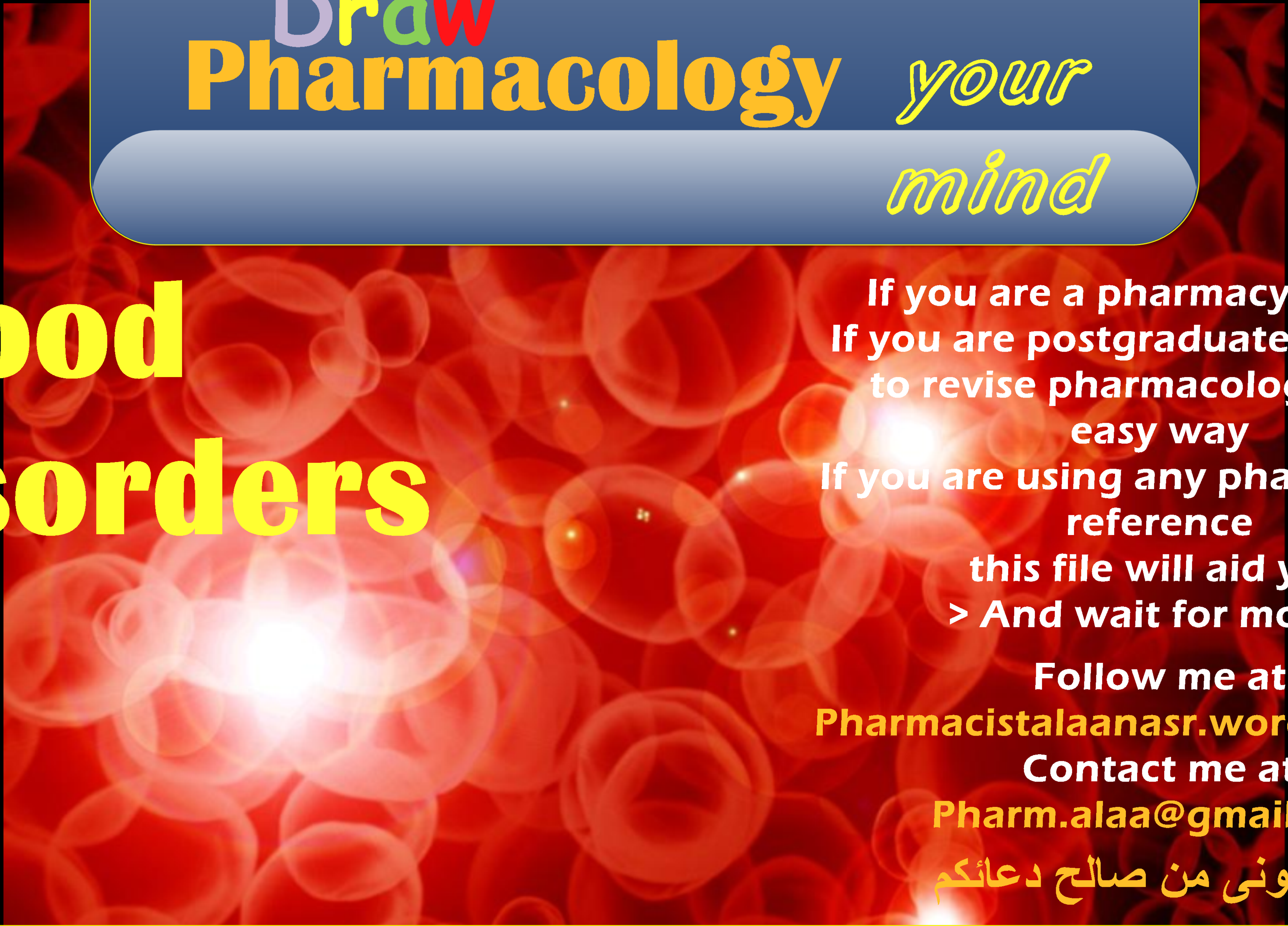
Draw Pharmacology in your mind

Blood disorders



If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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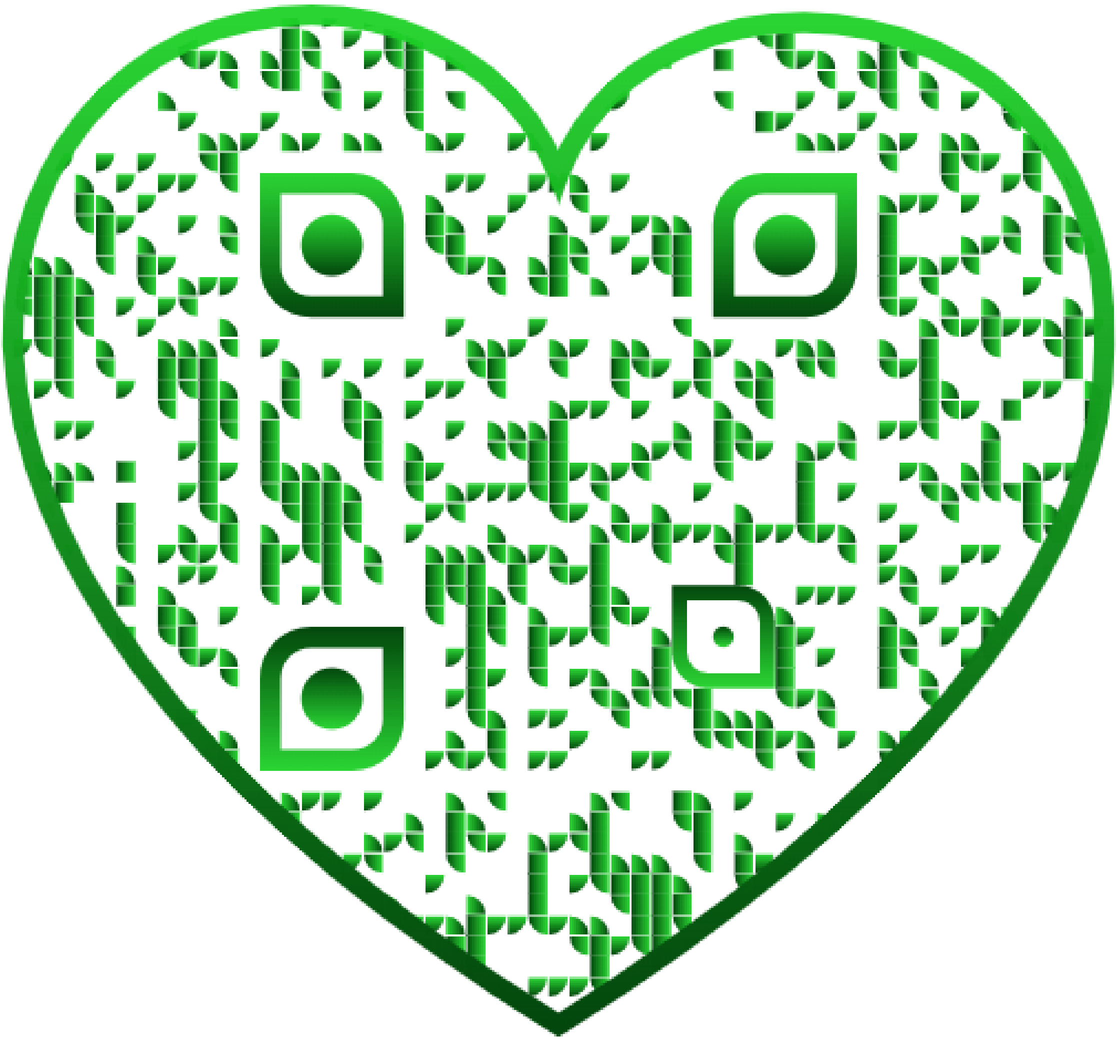
Contact me at
Pharm.alaa@gmail.com

لا تنسونى من صالح دعائكم

Pharmacist. Alaa Nasr د. آلاء نصر



- **Hemostasis** is the process of **maintaining** blood fluidity, repairing vascular injury and limiting blood loss while avoiding vessel occlusion "thrombosis" and inadequate perfusion of vital organs
- **Abnormalities of blood hemostasis** →

1. Thrombosis

2. Excessive bleeding

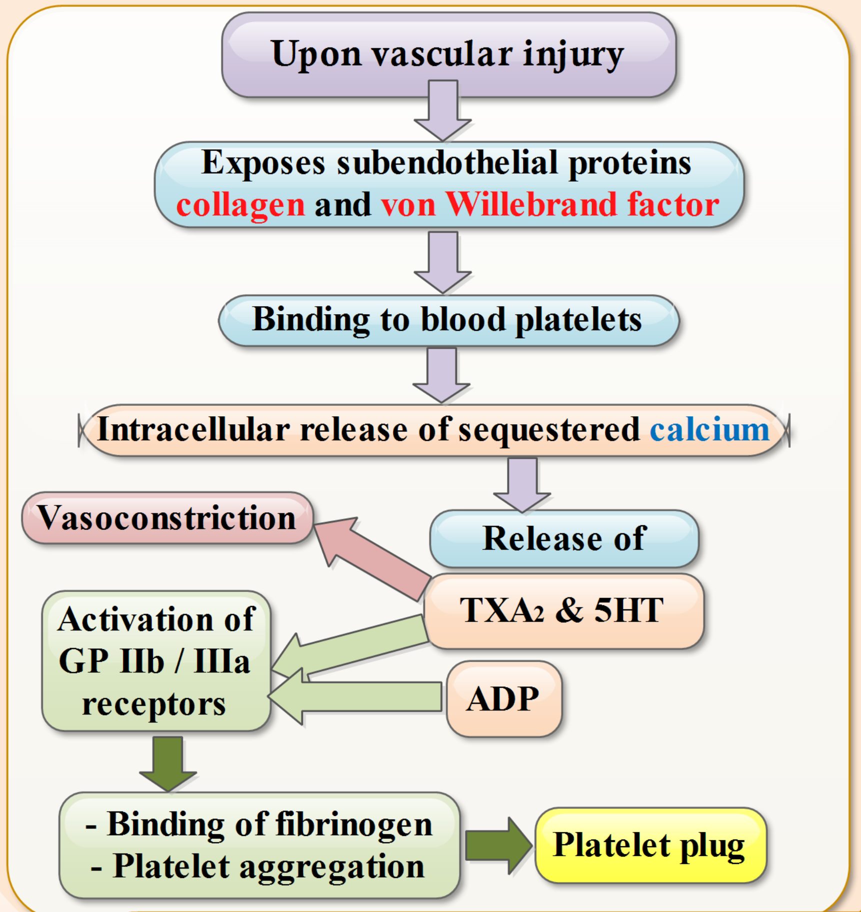
- **Note that ..** **Thrombosis** is the formation of unwanted blood clot that adheres to the wall of the blood vessel But an **Embolus** is a **floating** intravascular clot

What happens after a vascular injury ? How can the body maintain hemostasis ?

This is a complex process involves:

1. Vasoconstriction
2. Temporary blockage of a break by a platelet plug
3. Blood coagulation → formation of a clot that seals the hole until tissue is repaired *(coagulation is restricted to the site of injury by coagulation factors inhibitors)*
4. Fibrinolysis → Plug formation is accompanied by a local activation of a fibrinolytic pathway (Plasminogen → Plasmin)

Note.. Plasmin limits clot growth and dissolves fibrin network as the wound heals



Upon vascular injury

Exposes subendothelial proteins collagen and von Willebrand factor

Binding to blood platelets

Intracellular release of sequestered calcium

Release of

TXA2 & 5HT

ADP

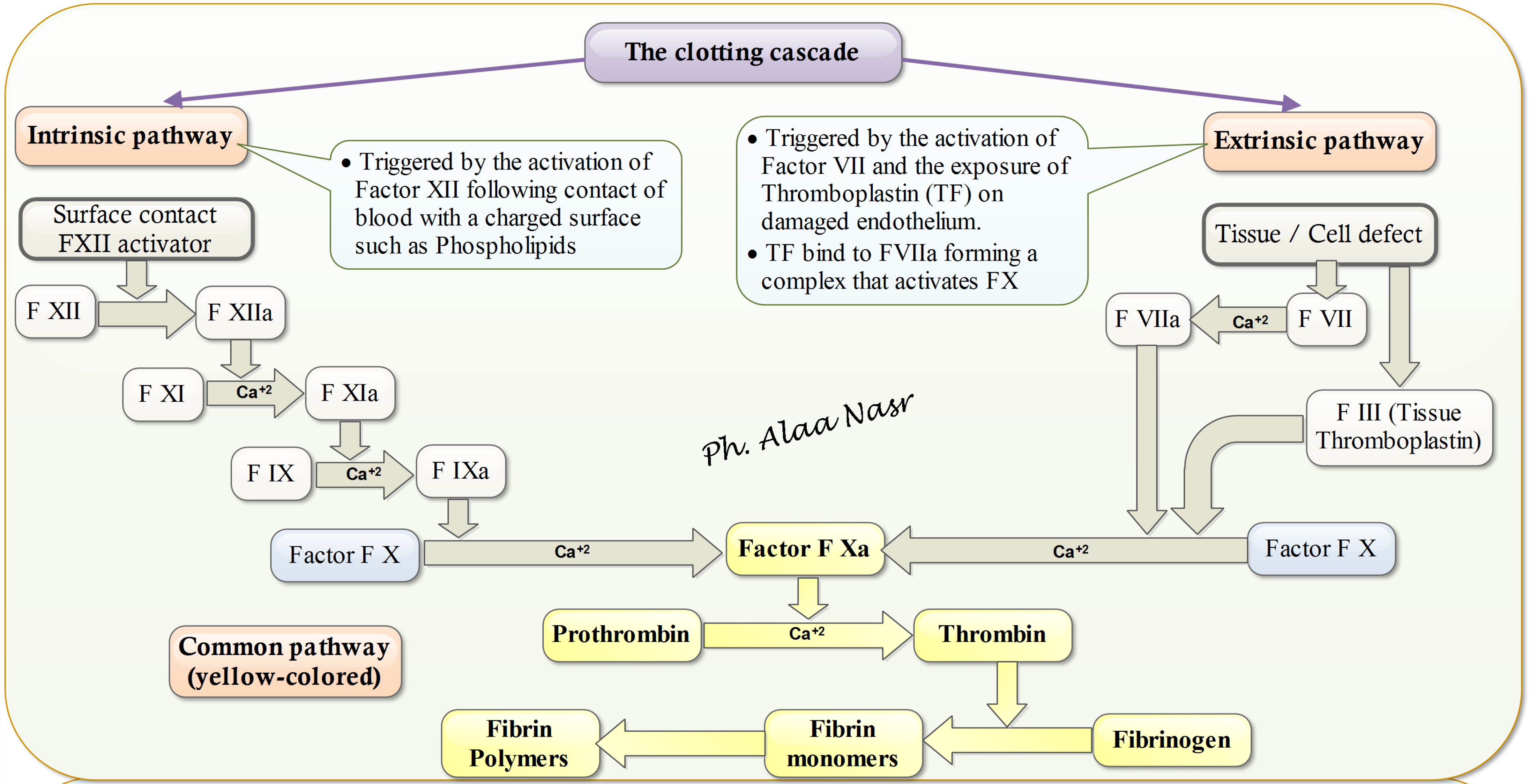
Vasoconstriction

Activation of GP IIb / IIIa receptors

- Binding of fibrinogen
- Platelet aggregation

Platelet plug

The clotting cascade



Intrinsic pathway

- Triggered by the activation of Factor XII following contact of blood with a charged surface such as Phospholipids

Extrinsic pathway

- Triggered by the activation of Factor VII and the exposure of Thromboplastin (TF) on damaged endothelium.
- TF bind to FVIIa forming a complex that activates FX

Surface contact FXII activator

F XII → F XIIa

F XI $\xrightarrow{Ca^{+2}}$ F XIa

F IX $\xrightarrow{Ca^{+2}}$ F IXa

Factor F X $\xrightarrow{Ca^{+2}}$ **Factor F Xa**

Tissue / Cell defect

F VII $\xrightarrow{Ca^{+2}}$ F VIIa

F III (Tissue Thromboplastin)

Factor F X $\xrightarrow{Ca^{+2}}$ **Factor F Xa**

Prothrombin $\xrightarrow{Ca^{+2}}$ **Thrombin**

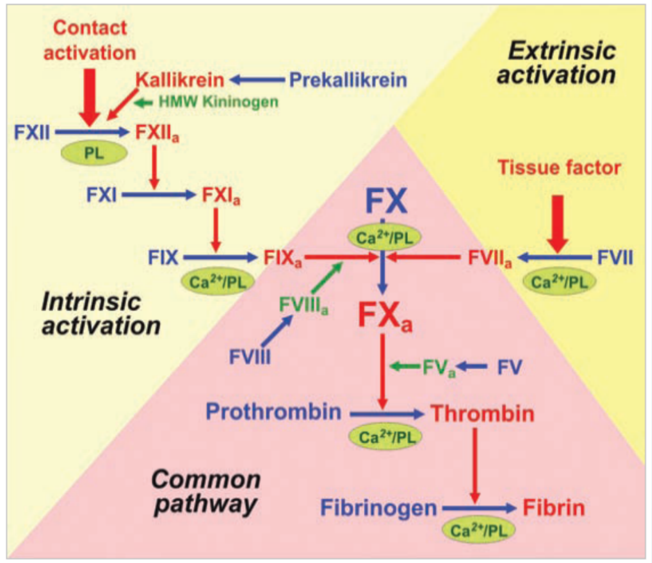
Fibrinogen → **Fibrin monomers** → **Fibrin Polymers**

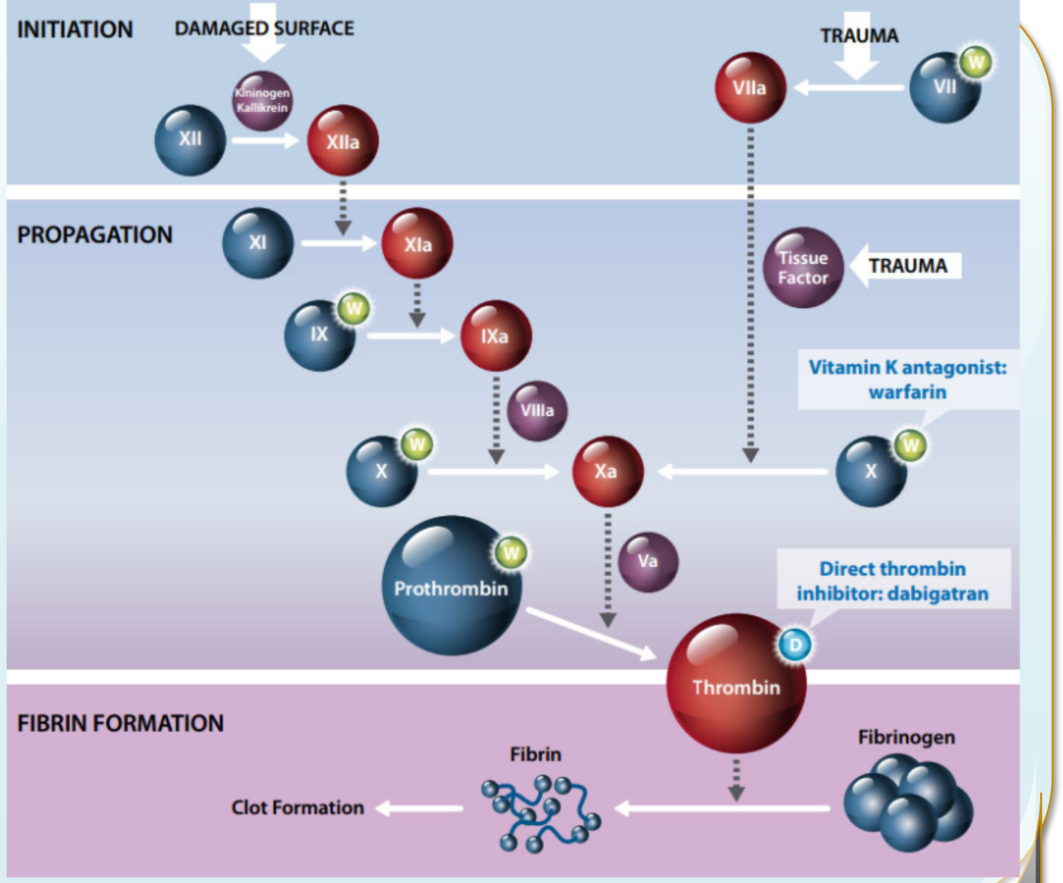
Common pathway (yellow-colored)

Note .. In Vitro

- Contact of shed blood with glass triggers the **intrinsic pathway**
- As Ca^{+2} is needed for activation of several clotting factors → so inactivation of Ca^{+2} using chelating agents such as → EDTA, Oxalate or Citrate → will prevent blood clotting in vitro

Note that .. This approach is not applicable in vivo


Contact activation
Kallikrein
Prekallikrein
HMW Kininogen
Extrinsic activation
FXII
PL
FXIIa
FXI
FXIa
Tissue factor
FX
Ca2+/PL
FIX
FIXa
FVIIa
FVII
Ca2+/PL
Ca2+/PL
Intrinsic activation
FVIIIa
FXa
FVIII
FVa
FV
Prothrombin
Thrombin
Ca2+/PL
Common pathway
Fibrinogen
Fibrin
Ca2+/PL


INITIATION
DAMAGED SURFACE
TRAUMA
Kininogen Kallikrein
XII
XIIa
VIIa
VII
W
PROPAGATION
XI
XIa
Tissue Factor
TRAUMA
IX
W
IXa
Vitamin K antagonist: warfarin
VIIIa
X
W
Xa
X
W
Prothrombin
W
Va
Direct thrombin inhibitor: dabigatran
D
Thrombin
FIBRIN FORMATION
Fibrin
Fibrinogen
Clot Formation

Blood hemostasis defects

1. Thrombosis

- The formation of unwanted blood clot that adheres to the wall of the blood vessel
- **This defect could be:**

Acquired
→ due to atherosclerosis

Genetic
→ due to
- Clotting factor inhibitor deficiency
- Decreased fibrinolysis

There is **more than one group** of drugs that can treat this defect

2. Hemorrhage

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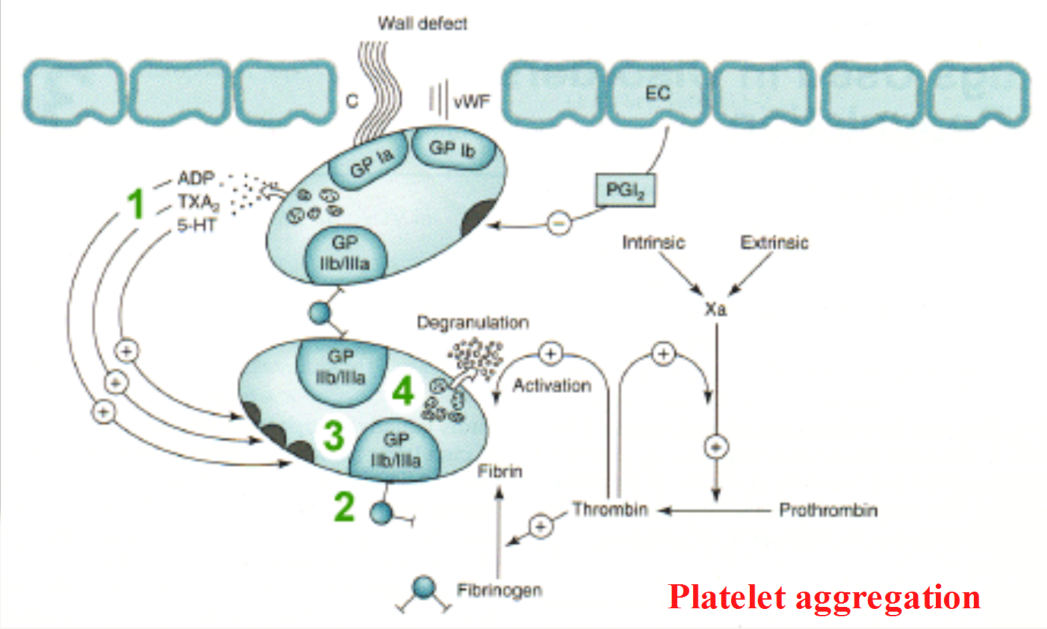
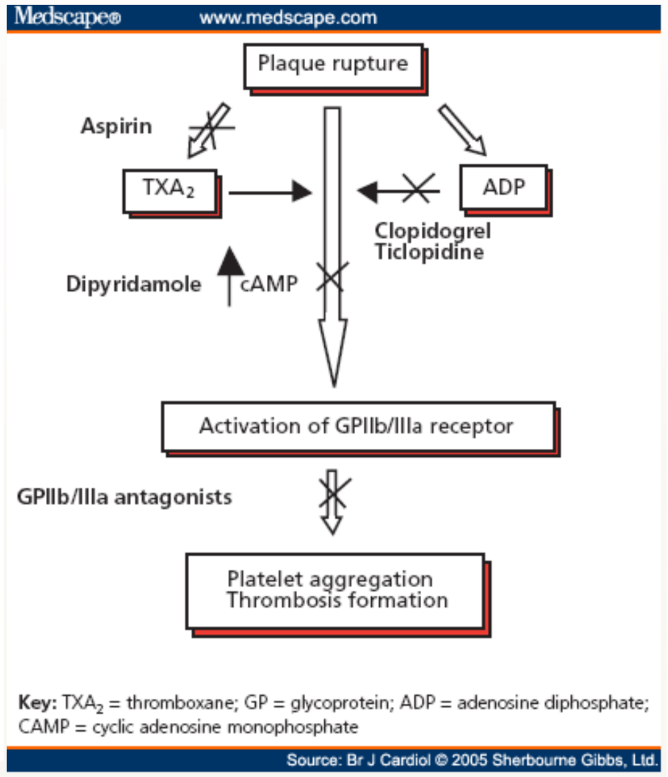
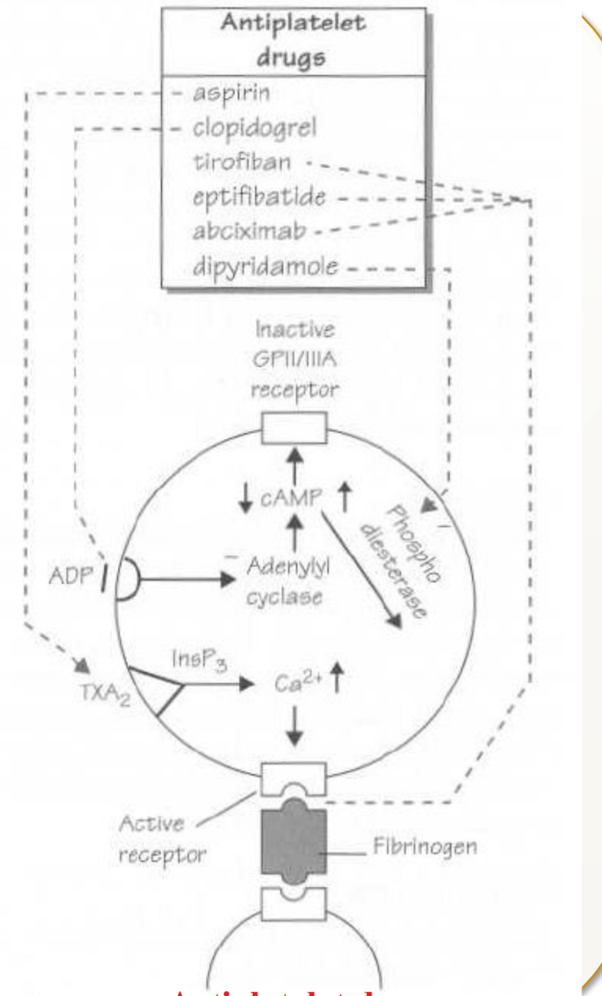

Wall defect
C
vWF
EC
GP Ia
GP Ib
PGI₂
1
ADP
TXA₂
5-HT
GP IIb/IIIa
Intrinsic
Extrinsic
Xa
Degranulation
Activation
4
3
Fibrin
2
Thrombin
Prothrombin
Fibrinogen

Platelet aggregation


Medscape®
www.medscape.com
Plaque rupture
Aspirin
TXA₂
ADP
Clopidogrel
Ticlopidine
Dipyridamole
cAMP
Activation of GPIIb/IIIa receptor
GPIIb/IIIa antagonists
Platelet aggregation
Thrombosis formation

Key: TXA_2 = thromboxane; GP = glycoprotein; ADP = adenosine diphosphate; CAMP = cyclic adenosine monophosphate

Source: Br J Cardiol © 2005 Sherbourne Gibbs, Ltd.


Antiplatelet drugs
aspirin
clopidogrel
tirofiban
eptifibatide
abciximab
dipyridamole
Inactive GPII/IIIA receptor
cAMP
Adenylyl cyclase
Phospho diesterase
ADP
TXA₂
InsP₃
Ca²⁺
Active receptor
Fibrinogen

Antiplatelet drugs

1) Platelet aggregation inhibitors

1. Aspirin

Aspocid
75 mg tablets
ASPOCID
INFANTILE

Mechanism

- Inhibit **Thromboxane synthesis** through irreversible acetylation (inhibition) of COX enzyme
- **Note that** .. this inhibition lasts for 7 - 10 days which is the life span of platelets

Adverse effects

1. Gastrointestinal bleeding
2. Increased risk of hemorrhagic stroke

Interactions

- **Celecoxib** (selective COX-2 inhibitor) reduce the effect of aspirin on platelet aggregation → through shifting balance towards the formation of Thromboxane A_2

Indications

- Indicated to decrease the incidence of recurrent **myocardial infarction**

JUSPRIN
Aggrex 75mg

2. Ticlopidine
3. Clopidogrel

Mechanism

- **Blocking ADP receptors** → so inhibit binding of ADP and the subsequent activation of GP IIb / IIIa receptors

Adverse effects

- Life threatening hematologic adverse effects such as:
→ Neuropenia , aplastic anemia

Indications

1. Used for patients with a history of cerebral thrombotic event
2. Used with Aspirin to prevent coronary stent thrombosis

Interactions

- Inhibit cytochrome P_{450} → so interfere with metabolism of several drugs such as:
→Phenytoin , Tolbutamide

Plavix
STROKA
CLOPEX

4. Eptifibatide
5. Tirofiban

Mechanism

- They are **blocker of glycoproteins IIb / IIIa receptors** → so inhibit binding of fibrinogen and the consequent platelet aggregation

6. Dipyridamole

Mechanism

- **Inhibit phosphodiesterase enzyme** → ⇑ cAMP which → ⇓ Ca^{+2} → ⇓ TXA_2
- Potentiate the effect of **prostacyclin** → ⇓ platelet aggregation

Indications

1. Used in combination with warfarin to inhibit embolism from prosthetic صناعى heart valves
2. Used in combination with 25 mg Aspirin for secondary prophylaxis of cerebrovascular diseases

Blood hemostasis defects

1. Thrombosis

There is **more than one group** of drugs that can treat this defect **(Continue ..)**

2) Anticoagulants

Indications

- Used in prevention and treatment of
  1. Acute venous thrombosis
  2. Pulmonary embolism
  3. Acute myocardial infarction
- Some are used to prevent thrombosis in dialysis machines

1. Heparin

- It occurs as a **macromolecule complex with Histamine** in mast cells
- **Commercial Heparin** is obtained from porcine خنزير intestine or bovine أبقار lung
- **Low molecular weight Heparin (LMWH)** is obtained by chemical or enzymatic depolimerization of unfractionated heparin **(ex. Enoxaparin** = Clexane® **)**

Mechanism

- **Bind to antithrombin III** and accelerate the rate of deactivation of clotting factors by 1000 fold
- So, serves as catalysts for the deactivation reaction

Cal-Heparine

Pharmacokinetics

- **Heparin** is given by **IV or SC** injection → gives its maximal effect within **1-2 hrs**
- **LMWH** is given by **SC** injection gives its maximal effect after **4 hrs**

→ **Note that**

1. This drugs should **not** be given by **IM** injection to avoid **hematoma**
2. They do not cross placental barrier → **safe for pregnant women**

CLEXANE
8000

Adverse effects

1. **Hemorrhage** → **treated by**:
   - a) Discontinuation of the drug
   - b) **Protamine Sulphate** → binds with heparin → forming inactive complex
2. **Hypersensitivity** → urticaria, chills or anaphylactic shock

2. Lepirudin

- A polypeptide closely related to **Hirudin**
- Obtained from the **saliva of medicinal leech**
- Produced from yeast by **recombinant technique**
- Given IV → half life 1 hr

Mechanism

A highly specific inhibitor of the thrombogenic activity of thrombin

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3. Warfarin

Mechanism

- It interfere with the cofactor function of vitamine K → so, prevents the formation of γ-carboxy glutamyl derivatives *(active form)* of factors (II , VII , IX , X) which can bind to Ca^{+2}
- It inhibits vit.K epoxide reductase enzyme and quinone reductase enzyme which are needed to regenerate reduced vit.K

Pharmacokinetics

Its effect **starts** after **8 - 12 hrs** after oral administration with a **peak** effect after **72 - 96 hrs** untill the circulating clotting factors are depleted

Adverse effects

Bleeding

If minor
- Treated by **oral** vitamin K

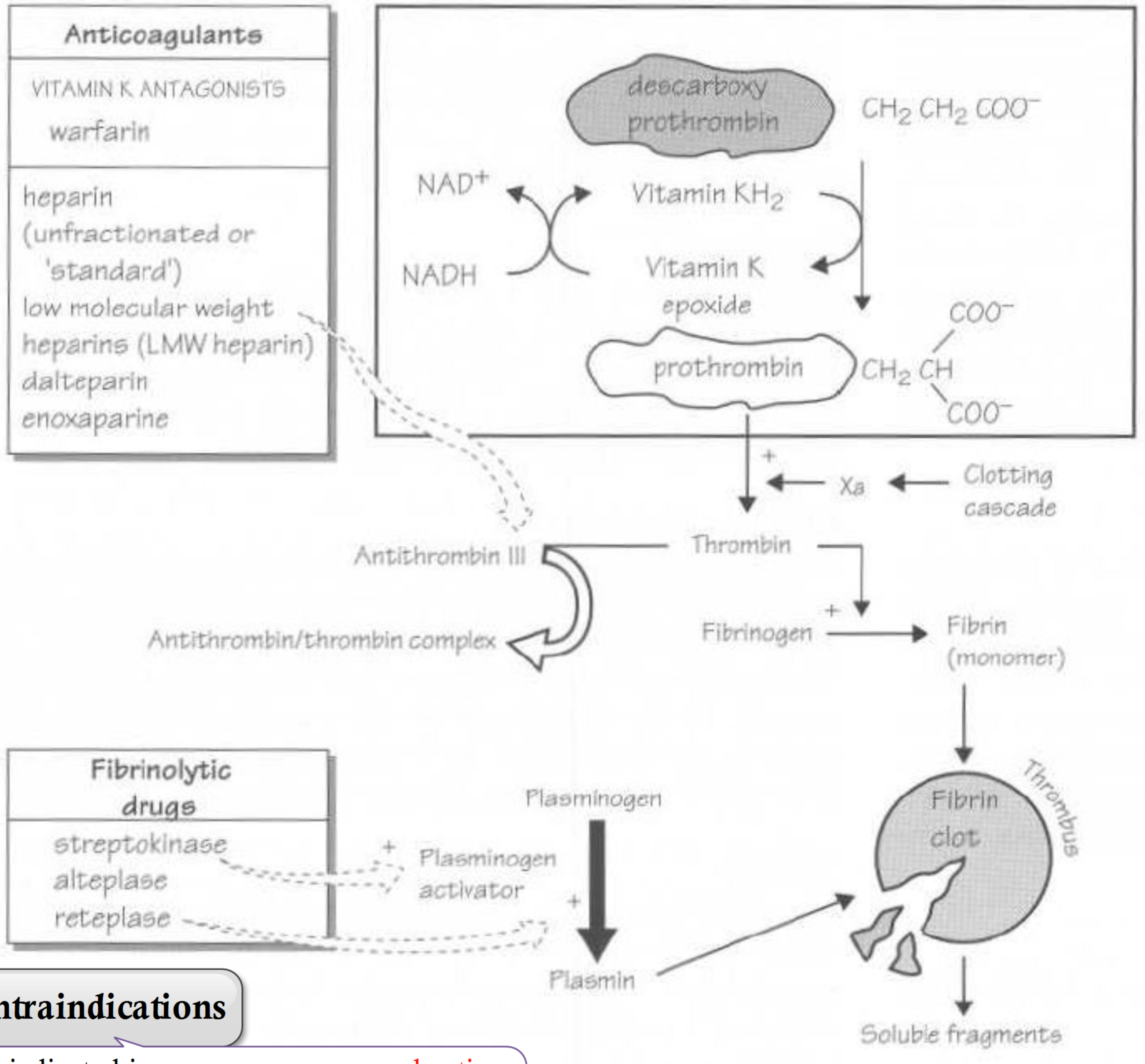
If severe
- Treated by **IV** vitamin K
- Transfusion of whole blood or frozen plasma or plasma concentrate of blood factors

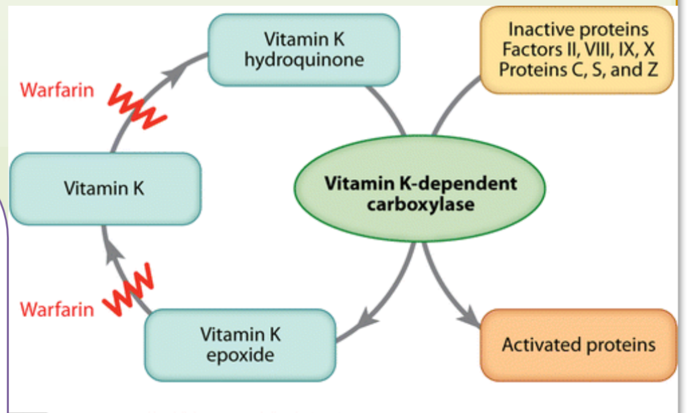
Contraindications

Contraindicated in **pregnancy** causes abortion and birth defects (abnormal bone formation)

Drug interaction

1. **Cimetidine** → LME inhibitor → inhibits Warfarin metabolism → so ⇑ its effect
2. **Sulphonamides** → displace Warfarin from plasma proteins binding (PPB) sites → so ⇑ its effect
3. **Aspirin** → inhibit platelet aggregation → so ⇑ Warfarin effect
4. **Phenylbutazone** → interferes with Warfarin's metabolism, PPB and inhibit platelet aggregation → so ⇑ its effect
5. **3rd generation Cephalosporins** → kill intestinal bacteria that synthesize vit.K → it also inhibit vitamine K epoxide reductase → so ⇑ its effect
6. **Barbiturates and Griseofulvin** → LME inducers → so ⇓ Warfarin effect


Anticoagulants
VITAMIN K ANTAGONISTS
warfarin
heparin
(unfractionated or
'standard')
low molecular weight
heparins (LMW heparin)
dalteparin
enoxaparine
descarboxy
prothrombin
CH2 CH2 COO−
NAD+
NADH
Vitamin KH2
Vitamin K
epoxide
prothrombin
CH2 CH
COO−
COO−
+
Xa
Clotting
cascade
Antithrombin III
Thrombin
Antithrombin/thrombin complex
Fibrinogen
+
Fibrin
(monomer)
Fibrinolytic
drugs
streptokinase
alteplase
reteplase
+
Plasminogen
activator
Plasminogen
+
Plasmin
Fibrin
clot
Thrombus
Soluble fragments


Vitamin K
hydroquinone
Inactive proteins
Factors II, VIII, IX, X
Proteins C, S, and Z
Warfarin
Vitamin K
Vitamin K-dependent
carboxylase
Warfarin
Vitamin K
epoxide
Activated proteins

Kamali F, Wynne H. 2010.
Annu. Rev. Med. 61:63–75

Marevan
tablets
1 mg
Warfarin
tablets BP 1mg
100 tablets
GlaxoWellcome
Marevan
tablets
3 mg
Warfarin
tablets BP 3 mg
100 tablets
GlaxoWellcome
Marevan
Tablets 5 mg
Warfarin
tablets BP 5mg
100 tablets

Blood hemostasis defects

1. Thrombosis

There is **more than one group** of drugs that can treat this defect **(Continue ..)**

3) Thrombolytics

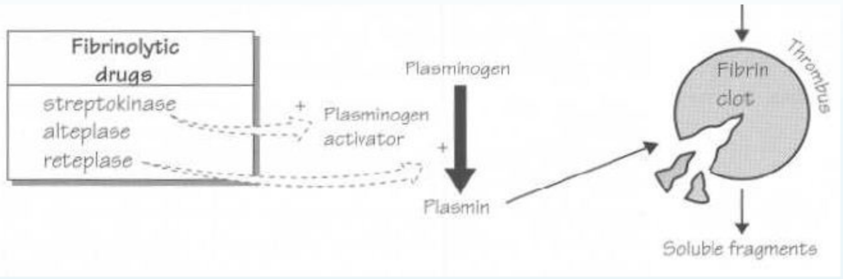
They can lyse both normal and pathological thrombi

Mechanism

- They **stimulate the fibrinolytic pathway** (conversion of plasminogen to plasmin)
- **Note that ..**

1. Clot dissolution is more efficient when treatment is initiated **early**

2. Should be **administered with Aspirin or Warfarin** to prevent the formation of other local thrombi



Uses

1. Used to dissolve clots in strokes
2. Used to restore catheter and shunt function

Contraindications

1. Pregnancy
2. Patients with healing wounds

Drug interactions

Metronidazole & Carbimazole → prolongs prothrombine time → *(it has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants)* → so, pateint will be susceptible to bleeding

1. Streptokinase

Extracellular protein obtained from cultured hemolytic streptococci

Mechanism

- It forms a **complex with plasminogen** → this complex →

1. Catalyze the activation of other plasminogen molecules into plasmin

2. Catalyze the degradation of fibrinogen and clotting factors V and VII

2. Alteplase

- Protease originally derived from cultured human melanoma cell

- Now it is obtained by recombinant technique

Mechanism

It activates plasminogen that is bound to fibrin in a thrombus

Note .. It is **superior** to streptokinase in dissolving **older clots**

2. Hemorrhage

This defect can be

Acquired

- Liver disease (site of clotting factor synthesis)
- Vitamine K deficiency
- Trauma
- Autoimmune disease (platelet distruction)
- Fibrinolytic or anticoagulant therapy

Genetic

- Platelet abnormalities
- Blood vessel wall abnormalities
- Clotting factor deficiency "Hemopilia A & Hemophilia B"
- Excess clot breakdown (fibrinolysis)

- **Hemophilia A & B** are caused by deficiency in factor VIII and IX respectively
- **Treatment**

1. Human derived factor VIII or factor IX concentrate
2. Recombinant factor VIII or IX
3. Gene therapy trials

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There is **more than one drug** that can treat this defect

1. Aminocaproic acid

Mechanism

They inhibit plasminogen activation

Uses

1. Adjunctive therapy in hemophilia
2. Therapy for bleeding from fibrinolytic drugs
3. Prophylaxis for rebleeding from intracranial aneurysms

Potential adverse effects

Thrombosis

2. Protamine sulphate

- Obtained from fish sperms and testes
- Binds with Heparin → forming inactive complex
- So used to **treat bleeding** caused by **Heparin**

Adverse effects

1. Hypersensitivity reaction
2. Bradycardia and hypotension when injected rapidly

Protamine 1000
Protamine hydrochloride
5000 IU/5 ml
Roche
1 ampoule of 5 ml

3. Vitamine K

- Used to **treat bleeding** resulting from **oral anticoagulants** (ex. Warfarin)
- **Note that ..**

1. Effect appears within 4 days → new coagulation factors are synthesized
2. If an immidiate responce is needed → plasma transfusion